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Chapter 8

Recent Advances in Stem Cell and Tissue Engineering

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Abstract

The clinical application of stem cells in tissue engineering and regeneration is becoming more significant. However, its application has been limited by issues like reproducibility of the stem cells, ethical concerns of harvesting some of these stem cells, and controlling the fate of stem cells in vitro and in vivo. The advent of tissue engineering and regeneration has led to the fabrication of advanced biomaterials and scaffolds with enhanced ability to mimic and control the cellular microenvironment similar to that of innate stem cell niche. Combining the use of stem cells with biomaterials and scaffolds especially synthetic hydrogels that have exhibited physicochemical abilities and properties similar to native niche can be the future of tissue engineering in terms of formation of new tissues like bones. Recently, there has an increase in the use of either endothelial progenitor cells (EPCs), induced pluripotent stem cells (iPSCs), or adult mesenchymal stem cells in preclinical studies: however this is yet to be transferred to clinical setups as there are limitations in terms of regulations and ethical considerations. The purpose of this review is to give comprehensive details about the application of stem cells in tissue engineering.

Keywords: endothelial progenitor cells, induced pluripotent stem cells, adult mesenchymal stem, tissue engineering, scaffolds

1. Introduction

Tissue engineering is a multidisciplinary science that applies the principles of bioengineering for the fabrication of new and improved biomaterials capable of maintaining and restoring the functionality of organs and tissues impaired by disease and trauma. This translational approach has been applied to develop and design patient-specific tissue grafts that mimic the functional properties of native tissues. Three important factors have been accredited to the success of tissue engineering: cocultured stem cells, signaling factor, and the bio-fabricated scaffold.

The stem cells are capable of differentiating into several types of tissues and organs, while the bio-fabricated scaffold provides structural support to the seeded stem cells. Signaling factors are responsible for influencing cell phenotype, metabolism, migration, and organization.

Stem cells are undifferentiated cells of embryonic, fetal origin, and they possess the ability to give rise to differentiated cells and then finally develop into organs. Stem cell characteristics include the ability to self-replicate and renew, clonage forming, and high potency ability [1]. In terms of the potency ability of stem cells, stem cells can be totipotent, could differentiate into any cell types (pluripotent) [2], and could differentiate into cells that arise from the three germ layers—ectoderm, endoderm, and mesoderm—from which organs develop [3].

Stem cells can be categorized broadly into embryonic and adult stem cells and are efficient cell sources for tissue regenerative applications. They have also been reported to have the abilities to promote tissue homeostasis, growth, and repair, thereby contributing importantly to tissue and organ regeneration [4]. Bio-fabricated scaffolds consist of decellularized biomaterials to provide structural and anatomical functions to the seeded stem cells, thereby resulting into successful formation of specific tissue. In support of the above report, Kang and colleagues demonstrated that decellularized scaffolds loaded with autologous adipose-derived stem cells (ADSCs) were efficient to repair cartilage defect in an animal model [5]. They concluded that decellularized scaffolds loaded with ADSC induced significant and improved cartilage tissue repair compared to native cartilage.

2. Mesenchymal stem cells seeded for bone tissue engineering

MSCs are stromal stem cells that are heterogeneous and are derived from several tissue sources that include adipose tissue [6], periodontal ligaments [7], bone marrow (**Figure 1**) [8], umbilical cord (UC) [9], placenta [10], and lungs [11]. MSCs express surface markers like CD73, CD44, CD90, and CD105. The most widely known and used MSCs are bone marrow MSCs and adipose tissue-derived MSCs isolated and purified from the bone marrow and adipose tissue, respectively. Briefly, the anatomy of the bone marrow is made up of the parenchyma and the stroma part. The parenchyma houses the hematopoietic stem cells, and the stoma part consists of the bone marrow stromal cells (MSCs) that have the capability to differentiate into several cell lines like osteoblasts, chondrocytes, adipocytes, etc. The clinical use of both bone-derived mesenchymal stem cells and adipose stem cells in bone tissue engineering has been reported using various models of bone regeneration such as osteogenesis [12, 13], long bone defects [14, 15], and calvarial defects [16, 17]. Furthermore, co-administration of stem cells with cytokines has been reported to be efficient in bone repair as cytokines and growth factors like stromal derived factor-1 (SDF-1) can lead to increased migration and homing of stem cells to the defected site [18]. In a similar report by Ho et al., they demonstrated that co-administration of stromal-derived factor-1 with BM-MSCs would indirectly enhance bone repair by improving migration of innate cells to the site of bone fracture. They concluded that BM-MSCs overexpressing SDF-1 were efficient in improving the new bone formation during the early stage of fracture healing compared to BM-MSC treatment alone [19]. Genes implicated in fracture healing such as osterix [20], hypoxia-inducible factor-1 [21], and BMP-7 [22] have all been reported to be efficient in bone formation when transfected with MSCs.

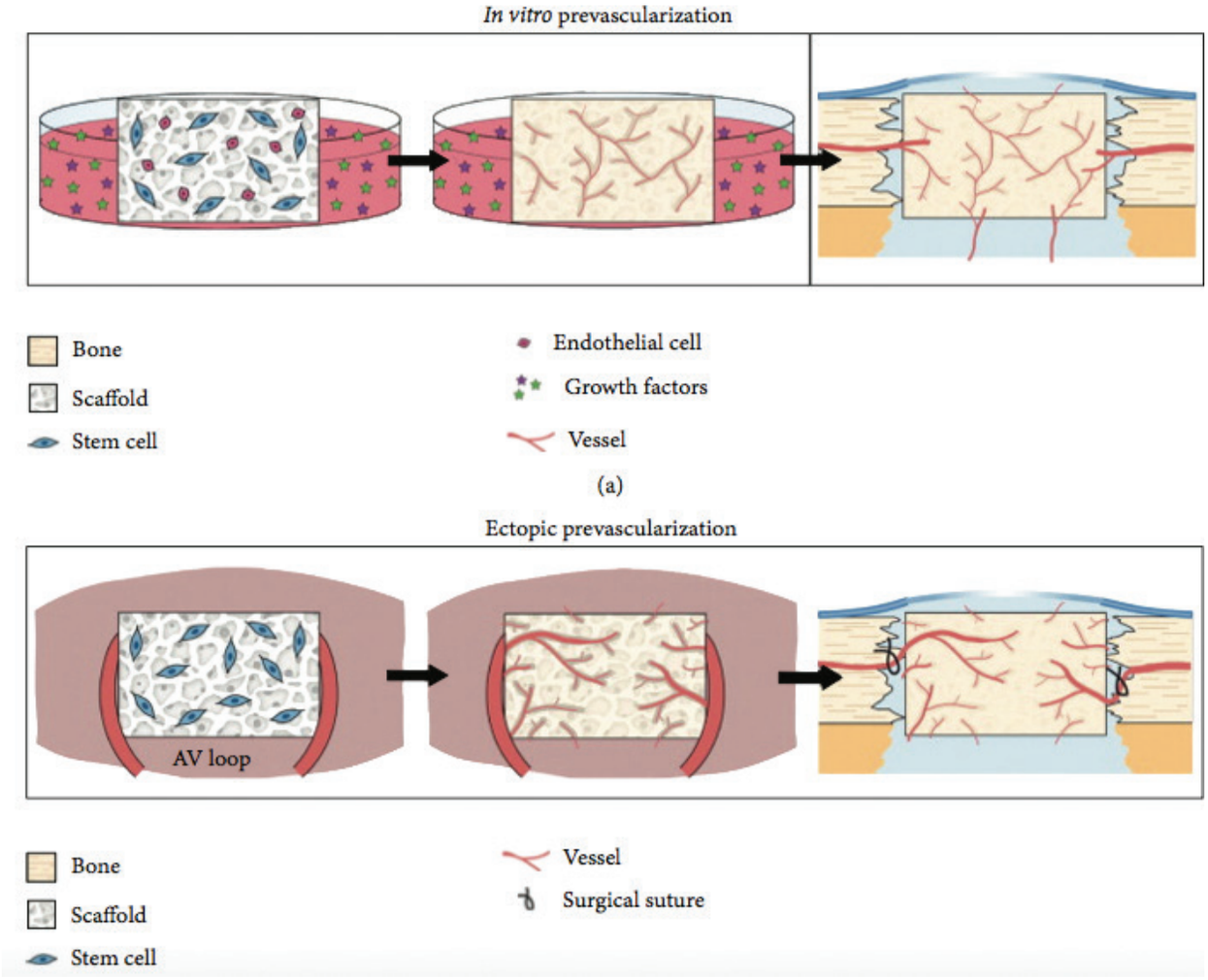

Figure 1. Showing in vivo and in vitro stem cell application in engineered tissue (a) In vitro prevascularization methods induce cell-seeded scaffolds to form vasculature (b) In vivo ectopic prevascularization involves implantation of a cell-seeded scaffold into a highly vascularized bed. Adapted from [26] with copyright permission.

3. Advances in MSCs and tissue engineering technology

Recently, bone tissue engineering in combination with novel stem cell-based technologies is yielding promising results as reported by Syed-Picard and colleagues in their experimental study that BM-MSC-derived cell sheets could be used to fabricate functional periosteal tissue [23]. Briefly, culturing BM-MSCs to hyperconfluence to produce abundant extracellular matrix to form robust cell sheets generated the BM-MSC-derived cell sheets. The authors reported that the generated cell sheets supported with calcium phosphate pellets were transplanted subcutaneously into mice for 8 weeks. They concluded that there was significant bone-like tissue formation by the BM-MSC-calcium phosphate pellet structure compared to the non-seeded calcium phosphate scaffold.

In another similar study by [24], BM-MSC cell sheet technology was compared to control cell complex. The authors reported that BM-MSC cell sheet resulted into significant expressed levels of growth factors crucial to bone development like vascular endothelial growth factor and PDGF. In another innovative study of stem cell application in tissue engineering, Ren et al. fabricated

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